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REMARKS

The Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Double Patenting

Applicants acknowledge and thank the Examiner for withdrawal of the double patenting rejection in view of the terminal disclaimer submitted on June 7, 2006.

Claim Rejections – 35 USC § 103

The Examiner rejects Claims 11-13, 16, 18-21 and 23-24 under 35 U.S.C. § 103(a) as being unpatentable over Tchaga et al. (WO 99/57992) in view of Porath et al. (Biochemistry, 1983: 22; p.1621-1630). The Applicants respectfully submit that the claims are patentable over the cited art for at least the reasons provided below.

In the prior Response, the Applicants submitted that Tchaga et al. teach adding an ion affinity peptide to the polypeptide of interest in order to efficiently complex metal ions, which increases specificity and adsorption affinity by preventing the participation of the native protein in adsorption. In contrast, Porath et al. describe the use of columns packed with chelator gels loaded with different metal ions in tandem in order to separate untagged serum proteins whose adsorption is mediated entirely by the native, i.e. untagged, protein.

In response to this argument made by the Applicants in the previous communication and reiterated herein, the Examiner states that it is irrelevant whether the protein is native or non-native, since either can be used in the protocol.

The Applicants respectfully submit that the Examiner's statement that either protein can be used in the protocol is demonstrably made from hindsight. There is no evidence of record, in either the cited references or the Office Action, that a method designed for use with ion affinity tagged proteins as taught by Tchaga et al. should be expected by one of ordinary skill to work with untagged proteins taught by Porath et al. The cited references teach the contrary.

Tchaga et al. is directed to the purification of a protein of interest using ion affinity tags, which constitute short polypeptide sequences that are designed to complex metal ions with much higher efficiency than the attached native polypeptide (please consult Tchaga et al., page 6, line 20 through page 7, line 4). The result is that the affinity of the fusion protein for the chromatographic column is mediated entirely by the metal ion binding capacity of the affinity tag itself, rendering the affinity for the column of the attached native polypeptide sequence irrelevant to the purification method (please consult Tchaga et al., page 2, lines 15-20).

In contrast, Porath et al. is directed to the purification of polypeptides to which no ion affinity tag has been fused, i.e. native, untagged proteins. Therefore, the purification process taught by Porath et al. depends entirely upon the affinity of various features of the native polypeptide sequence itself for the ion-loaded column (please consult Porath et al., page 1628, paragraph 8, *"Some Notes on the Adsorption Mechanism"*).

Accordingly, whereas the method taught by Tchaga et al. purification must distinguish between tagged and untagged proteins, the tandem chromatography taught by Porath et al. must distinguish among native proteins, many of which may share comparable affinities for chelated metal ions.

Put simply, while both methods are broadly directed to "purifying a protein of interest," the methods address two distinct problems: Tchaga et al. that of using and maximizing the ion affinity of a polypeptide sequence specifically designed to bind metal ions (Tchaga et al., page 2, lines 15-20), and Porath et al. that of optimizing column conditions to isolate proteins whose metal-binding determinants are variable or unknown (Porath et al., page 1628, paragraph 8; page 1629, left column).

As such, the ordinarily skilled artisan would find no reason to combine the teachings of Tchaga et al. with those of Porath et al., since there is no reason to expect that a method directed to the purification of untagged proteins would provide an improvement in the purification of ion binding peptide-tagged proteins. The only document of record which teaches the success of such an approach is the instant Application.

Further in response to arguments made by the Applicants in the previous communication and reiterated herein, the Examiner states, without evidentiary support, that "purification of proteins usually occurs in the presence of different columns ... and the use of additional columns (in tandem, for example) or different ions in the protocol is dictated by the need to optimize the conditions for most efficient and maximum recovery of the protein of interest" (Office Action, page 4). As provided for in MPEP 2144.03, "Reliance on Common Knowledge in the Art or 'Well Known' Prior Art", the Examiner is respectfully requested to provide evidence or an affidavit of personal knowledge as to why the person of ordinary skill would conclude such. The Applicants further submit that this reasoning is not applicable to the suggestion to combine references which teach different types of protein purification.

The Examiner states that it is irrelevant that Porath et al. refers to untagged proteins, since the idea is to use metal ion affinity chromatography to purify a protein of interest. The Applicants respectfully submit that the tagged status of the protein is directly relevant because it is a limitation recited in the claims.

Claim 1 recites a recombinant vector comprising a nucleotide sequence encoding "a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for said metal ion affinity peptide." As such, the claims are drawn to tagged proteins. Accordingly, the tagged status of the protein is relevant.

The Examiner responds to argument made by the Applicants in the previous communication regarding the differing principles at work in the purification schemes by stating, without evidentiary support, that "maximizing specificity and high-efficiency recovery go hand in hand in protein purification since, maximum specificity can cause high-efficiency of recovery, as it is desired when using any purification kit" (Office Action, page 5). Again as provided for in the rules, the Examiner is respectfully requested to provide evidence or an affidavit of personal knowledge as to why the person of ordinary skill would conclude such. Applicants further submit that it is unclear why a relationship between specificity and high-efficiency recovery should be assumed to be identical for the tagged and untagged proteins as taught in the cited references.

Moreover, in responding to the Applicants' prior argument that there is no motivation to combine the cited references to be found in the references themselves, the Examiner merely reiterates what each reference teaches without showing where any motivation to combine is taught in those references or elsewhere (Office Action, pages 5-6). The Applicants respectfully submit that the cited references are directed to two different strategies of protein purification, which were not combined in any document of record from the period of 1983 to 1998 for the reason that one of skill in the art had no reason to expect success in applying a strategy for purifying untagged proteins to a method teaching the use and optimization of ion-binding tags.

Further, the instant claims are non-obvious over the combination of cited references as *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*,730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984) applies.

In *Lindemann*, a hydraulic scrap-processing machine capable of processing light and heavy scrap metal was declared in a reversal to be non-obvious over prior art describing machines which processed only light or heavy scrap respectively, although both of those technologies were old and well-known to the art. An invention is not obvious where 'old' or 'well known' elements solve different problems (i.e. processing of light vs. heavy scrap, or purification of untagged proteins vs. ion binding peptide-tagged proteins).

Accordingly, for at least these reasons Claims 11-13, 16, 18-21 and 23-24 are patentable under 35 U.S.C. § 103(a) over Tchaga et al. (WO 99/57992) in view of Porath et al. (Biochemistry, 1983: 22; p.1621-1630). Reconsideration and withdrawal of the rejection is respectfully requested.

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CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CLON-056US2.

Respectfully submitted,

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Date: November 3, 2006

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